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EFFECTS OF METHYLMERCAPTOIMIDAZOLE (MMI), PROPYLTHIOURACIL (PTU), POTASSIUM PERCHLORATE ($KClO_4$) AND POTASSIUM IODIDE (KI) ON THE SERUM CONCENTRATIONS OF THYROTROPHIN (TSH) AND THYROID HORMONES IN THE RAT

By

P. T. Männistö[1], T. Ranta[2] and J. Leppäluoto[3]

ABSTRACT

Male Sprague-Dawley rats were given graded doses of methylmercaptoimidazole (MMI), propylthiouracil (PTU), $KClO_4$ or KI in drinking water for 4 days, or the lowest effective dose of each drug for various times. The rats were sacrificed at 1–2 p. m. and serum T_3, T_4 and TSH concentrations were measured by radioimmunoassays. It was found that administration of 5 mg/l of MMI, 10 mg/l of PTU and 100 mg/l of $KClO_4$ for 4–14 days induced a transient rise in serum TSH and a fall in serum T_3 or T_4 or in both. The effects of KI were not consistent. In another series of experiments, PTU (10 mg/l) was given in drinking water for 4 days, and then graded doses of T_3 or T_4 were given iv, or 100 ng of TRH was injected into a tail vein, or the animals were exposed to 4°C for 30 min. The initial high TSH levels were further increased by TRH and cold and decreased by T_3 and T_4. The PTU-treated animals had goitres after 4 days. We infer that low doses, that is to say 10–100 times lower than previously described, of antithyroid drugs induce a hypothyroidism characterized by an increased TSH level and a decreased serum T_3 or T_4 level or both. A 4 days' treatment with PTU (10 mg/l in tap water) is a suitable tool for studying the effect of various conditions on TSH secretion.

The effects of various antithyroid drugs are well documented at the level of the thyroid gland (*Stanley & Astwood* 1947; *Richards & Ingbar* 1959; *Iino et al.* 1961; *Hershman & Van Middlesworth* 1962; *Nagataki & Ingbar* 1964; *Wolff* 1964). However, their effects on the serum concentrations of immunoassayable T_3, T_4 and TSH have been less widely studied. In most of the previous studies only one, and evidently a high concentration of an antithyroid drug has been used, resulting in at least temporarily increased secretion of TSH (*Bakke & Lawrence* 1964; *Wilber & Utiger* 1967; *Liewendahl et al.* 1972; *Griessen & Lemarchand-Béraud* 1973; *Saberi et al.* 1975).

The effects of suprapituitary factors on the regulation of TSH are usually studied in situations where the secretion of TSH is stimulated. We have previously stimulated TSH secretion in rats by cold-exposure (*Leppäluoto et al.* 1974; *Tuomisto et al.* 1975; *Ranta et al.* 1977) and found that it is possible to modify the stimulated TSH secretion by various drugs influencing central neuro-transmission (*Tuomisto et al.* 1975; *Ranta et al.* 1977; *Männistö et al.* 1979). In other studies TSH secretion was stimulated by thyroidectomy but the very high TSH levels were not changed by drugs (*Mueller et al.* 1976) or by cold-exposure (*Männistö*, unpubl. results).

To find another reliable system for the stimulation of TSH secretion and to elucidate the acute effects of various antithyroid drugs, we measured serum concentrations of T_3, T_4 and TSH by specific radioimmunoassays in a series of experiments where graded doses of four antithyroid drugs were given to the rats in tap water for 4 days. In the further studies a low effective dose of each drug was given for varied periods of time. We were able to show that very low concentrations of antithyroid drugs effectively stimulated TSH secretion. The elevated TSH levels responded to exposure to cold, to thyroid hormones and to TSH-releasing hormone.

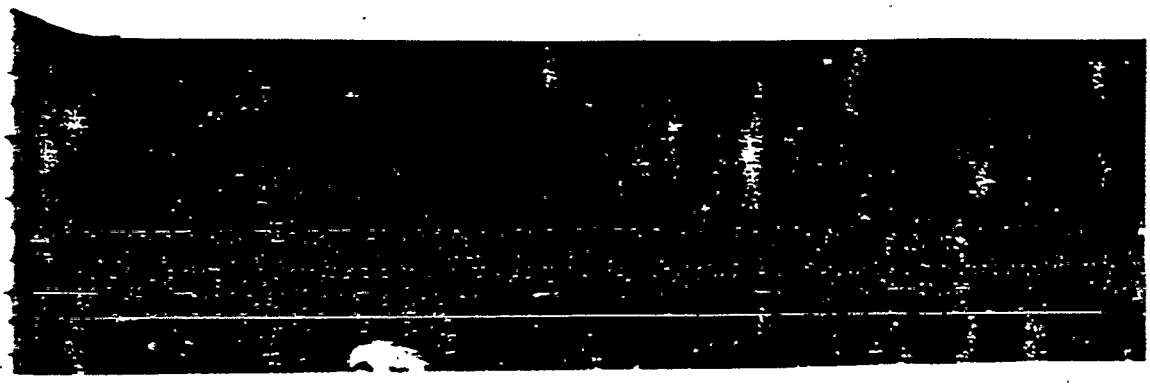
MATERIAL AND METHODS

Animals

Male outbred Sprague-Dawley rats weighing 150–220 g at the beginning of the experiments were used. They were kept 2–5 animals per cage and fed tap water and pellets (iodine concentration 0.5–1 mg/kg) *ad libitum*. The animal room was artificially illuminated from 7 a.m. to 7 p.m. and kept at 20–22°C. The animals were decapitated between 1 p.m. and 3 p.m.

Experimental designs

1. *Studies with various doses of propylthiouracil (PTU), methylmercaptoimidazole (MMI), $KClO_4$ and KI* – In the *first* series of experiments graded doses of PTU (0, 1, 5, 10, 25 and 50 mg/l), MMI (0, 1, 5, 10 and 25 mg/l), $KClO_4$ (0, 10, 50, 100 and 500 mg/l) and KI (0, 10, 100 and 1000 mg/l) in tap water were given to groups of 5–6



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L AND METHODS

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opylthiouracil PTU), *methylmercaptoimidazole*
series of experiments graded doses of PTU (
5, 10 and 25 mg/l), $KClO_4$ (0, 10, 50, 100 and
mg/l, in tap water were given to groups of 5–

rats for 4 days, beginning at 1 p.m. on the first day. The consumption of drinking fluid was similar in all the groups. The daily dose of each drug at 10 mg/l level varied from 0.5 to 1.7 mg. All animals gained weight similarly and were apparently healthy. The animals were decapitated on the 5th day at 1–3 p.m. and the whole trunk blood was collected for the measurement of serum T_3, T_4 and TSH concentrations (cf. below).

In the *second* series of experiments PTU (10 mg/l), MMI (5 mg/l), $KClO_4$ (100 mg/l, and KI (100 mg/l were given in tap water as above and the animals ($n = 5$–7 in each group were decapitated on the 2nd, 4th, 6th, 9th and 14th day at 1–3 p.m. One or two control rats were killed at each point of time (total 6–8 controls per each drug).

In the *third* experiment PTU (10 mg/l) was given in drinking water as above and on the 4th ($n = 9$) and 10th day ($n = 6$) the animals were decapitated. The control rats ($n = 6$) were killed on the 10th day. The thyroid glands and adenohypophyses were excised and weighed.

2 Effects of cold, TRH and thyroid hormone treatment on TSH concentration in the 4-day PTU treated rats. – In the *first* series of experiments the reproducibility of the PTU-induced TSH response was studied. PTU (10 mg/l) was given in drinking water for 3 or 4 days and then the animals were decapitated for the measurement of serum TSH. The experiments (5–7 rats in each) were repeated 5 times and the coefficients of variation in the final serum TSH concentrations were calculated.

In the *second* experiment PTU (10 mg/l) was given in drinking water as above. On the 4th day 10 rats were transferred to a room with a temperature of 4°C for 30 min and then sacrificed for measurement of serum TSH. Other 10 rats were given 100 ng of TRH into a tail vein and the animals were decapitated 10 min later. The control animals ($n = 10$) received saline iv and were decapitated at the same time. The fourth group of rats ($n = 10$) received water instead of PTU.

In the *third* experiment 60 rats received PTU (10 mg/l) as above for 4 days. Then graded doses of T_3 (0, 1.25, 2.5, 5, 12.5 or 125 μg/kg) or T_4 (5, 25, 37.5, 50, 100 or 125 μg/kg) were injected into the tail vein. The rats were decapitated 2 h later for measurement of serum TSH. This time interval has been found suitable in an earlier study in rats (*Wilber & Utiger* 1967).

Hormones and drugs

Thyroxine, triiodothyronine, propylthiouracil, methylmercaptoimidazole, $KClO_4$ and KI were purchased from Sigma (St. Louis). TSH-releasing hormone was obtained from Calbiochem (San Diego).

Radioimmunoassays of serum T_3, T_4 and TSH

T_3 and T_4 antisera were purchased from Farmos (Turku). T_3 antiserum had a cross-reactivity of < 0.01 % against mono- or diiodotyrosine and 0.15 % against T_4. T_4 antiserum had a cross-reactivity of < 0.01 % against iodotyrosines and 0.55 % against T_3. ^{125}I-labelled T_3 and T_4 were purchased from Amersham, England. A 100 μl serum sample was incubated overnight with antiserum and tracer at 4°C in a buffer containing anilinonaphtalen-sulphonate. The immunocomplex was precipitated with polyethyleneglycol (final concentration 12.5 % w/v). Serum TSH was measured with a rat TSH kit obtained as a gift from NIAMDD. A rat TSH preparation RP-1 was used as a standard (*Ranta* 1975).

Effects of graded doses of antithyroid drugs, administered for 4 days, on serum T_3, T_4 and TSH concentrations

PTU. – At the PTU level of 1 mg/l there were no significant changes in serum hormone levels in 4 days. At 5 mg/l serum TSH rose from 580 to 1730 ng/ml ($P < 0.05$) and remained at about that level at higher doses. Statistically significant falls in serum T_3 and T_4 occurred at 10 mg/l or at higher doses (Fig. 1).

MMI. – MMI did not affect serum hormone concentrations at 1 mg/l dose level in 4 days. At 5 mg/l serum TSH increased from 640 to 2180 ng/ml ($P < 0.01$) whereas serum T_3 and T_4 were not significantly affected. At 10 and 25 mg/l level of MMI, serum TSH was still high but declining. Serum T_4 concentrations decreased from 52 to 37 nmol/l at 10 mg/l ($P < 0.05$) and to 32 nmol/l at 25 mg/l ($P < 0.01$). The serum T_3 concentrations remained unchanged at all MMI dose levels (Fig. 2).

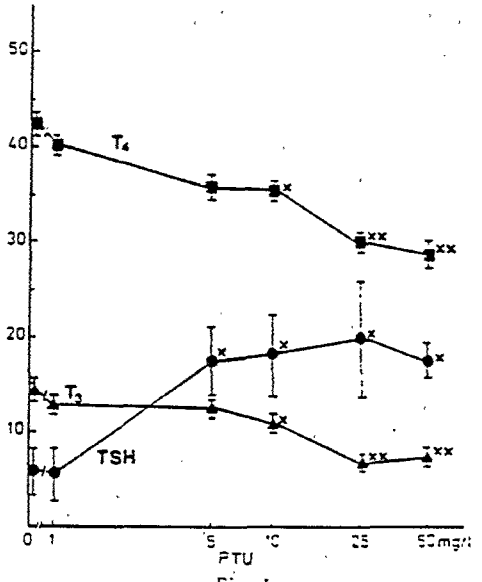
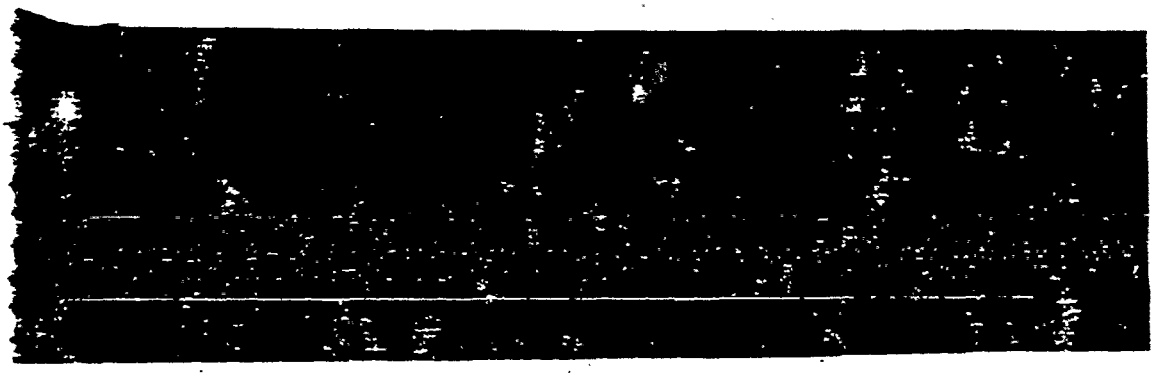


Fig. 1.

Serum T_3 (▲—▲: 10^{-1} nmol/l), T_4 (■—■: nmol/l) and TSH (●—●: 10^2 ng/ml) concentrations as a function of the PTU dose (mg/l in drinking water; log scale) in the rat. Mean ± SEM. n = 5–6. Statistics: × $P < 0.05$, ×× $P < 0.01$ vs. the water controls.



RESULTS

...id drugs, administered for 4 days.
...tions

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At 5 mg/l serum TSH rose from 580 to ...
at about that level at higher doses. Sta...
T_3 and T_4 occurred at 10 mg/l or at hi...

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... The serum T_3 concentrations remained ...
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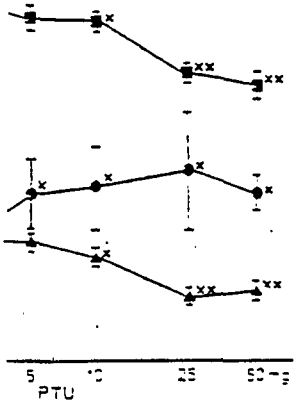

Fig. 1.

...■—■: nmol/l) and TSH (●—●: 10^2 ng/ml) ...
...TU dose (mg/l in drinking water: log scale) in ...
... × $P < 0.05$, ×× $P < 0.01$ vs. the water controls.

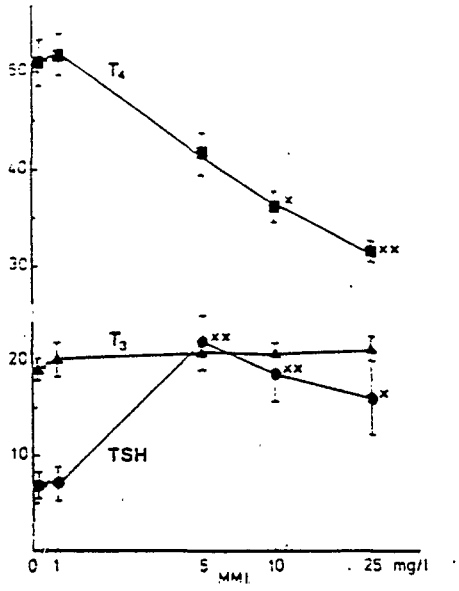

Fig. 2.

...erum T_3, T_4 and TSH concentrations as a function of the dose of MMI (mg/l in drinking water; log scale). For further information, see Fig. 1.

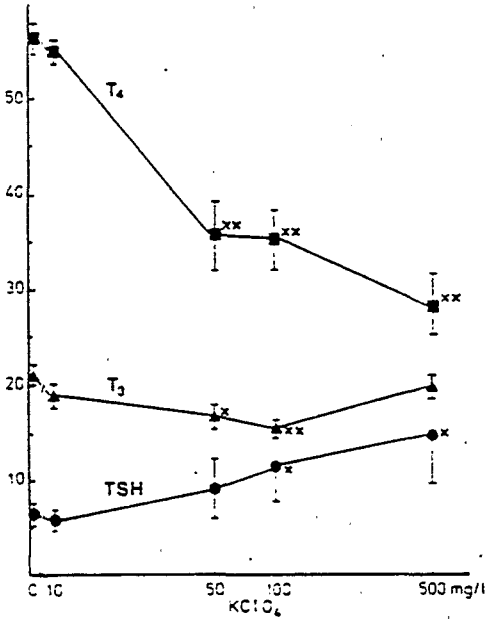

Fig. 3.

...erum T_3, T_4 and TSH concentrations as a function of the $KClO_4$ dose (mg/l in drinking water; log scale). For further information, see Fig. 1.

Table I.

Serum T_4 (nmol/l), T_3 (nmol/l) and TSH (ng/ml) concentrations as a function of ti during PTU (10 mg/l), MMI (5 mg/l), $KClO_4$ (100 mg/l) and KI (100 mg/l) treatme The drugs were given in tap water.

	Duration of the treatment, days					
	0	2	4	6	9	14
T_4, nmol/l						
PTU	50.0 ± 4.0	54.3 ± 5.5	38.0 ± 7.0*	27.4 ± 4.1**	12.1 ± 1.6**	34.8 ± 4.3
MMI	50.8 ± 3.1	49.0 ± 3.2	45.4 ± 2.8	36.8 ± 4.1*	–	34.7 ± 1.2
$KClO_4$	52.1 ± 6.8	40.8 ± 2.6	47.5 ± 2.7	45.4 ± 2.5	–	–
KI	69.4 ± 3.0	45.1 ± 3.2	63.5 ± 2.9	74.8 ± 0.9*	61.8 ± 4.3	82.7 ± 5.2
T_3, nmol/l						
PTU	1.8 ± 0.8	0.5 ± 0.07**	0.7 ± 0.14*	0.6 ± 0.08**	0.6 ± 0.13**	0.8 ± 0.1
MMI	2.0 ± 0.12	2.4 ± 0.12	2.1 ± 0.21	1.9 ± 0.15	–	2.3 ± 0.2
$KClO_4$	2.0 ± 0.10	2.1 ± 0.16	1.6 ± 0.11	1.6 ± 0.06	–	–
KI	2.8 ± 0.22	1.8 ± 0.07*	2.5 ± 0.16	2.9 ± 0.10	2.2 ± 0.07	2.7 ± 0.1
TSH, ng/ml						
PTU	520 ± 60	980 ± 100*	1400 ± 75*	2450 ± 350**	4550 ± 410**	1500 ± 350
MMI	505 ± 130	750 ± 20	2300 ± 250**	990 ± 170*	–	800 ± 250
$KClO_4$	610 ± 110	720 ± 160	1120 ± 100*	1095 ± 140	–	1200 ± 150
KI	650 ± 50	1460 ± 240*	1340 ± 280	1090 ± 230	1850 ± 300	570 ± 50

Mean ± SEM. n = 5–8. Statistically significant changes from the control values (= 0 da are shown as follows: * $P < 0.05$, ** $P < 0.01$.

$KClO_4$. – At 10 mg/l dose level serum hormones were unchanged, but a 50 mg/l T_3 fell from 2.1 to 1.7 nmol/l ($P < 0.05$) and serum T_4 from 56 t 36 nmol/l ($P < 0.01$). Similarly, T_4 remained low at 100 and 500 mg/l dos level and T_3 at 100 mg/l dose level. Serum TSH rose at 100 mg/l from 61 to 1170 ng/ml ($P < 0.05$) and continued to rise to 1490 ng/ml at 500 mg ($P < 0.01$) (Fig. 3).

KI. – There were no statistically significant changes in the hormone concen trations at 10–1000 mg/l dose levels of KI in 4 days (data not shown).

Serum T_3, T_4 and TSH concentrations during administration of the four antithyroid drugs for various times

PTU. – When PTU (10 mg/l) was given, serum T_3 fell on the 2nd day fror 1.8 to 0.5 ng/ml ($P < 0.01$) and remained at this low level for several day

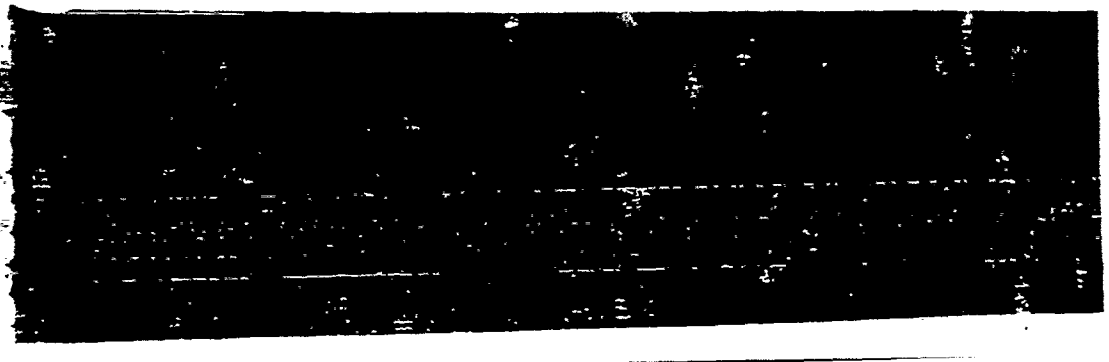

Table 1.

: TSH ng ml concentrations as a function ... $KClO_4$ 100 mg/l) and KI 100 mg/l) tre... were given in tap water.

Duration of the treatment, days			
4	6	9	1...
38.0 ± 7.0*	27.4 ± 4.1**	12.1 ± 1.6**	34.8 ± ...
45.4 ± 2.5	36.5 ± 4.1*	–	34.7 ± ...
47.5 ± 2.7	45.4 ± 2.5	–	
63.5 ± 2.9	74.8 ± 0.9*	61.5 ± 4.3	82.7 ± ...
0.7 ± 0.14*	0.6 ± 0.08**	0.6 ± 0.13**	0.8 ± ...
2.1 ± 0.21	1.9 ± 0.15	–	2.5 ± ...
1.6 ± 0.11	1.6 ± 0.06	–	
2.5 ± 0.16	2.9 ± 0.10	2.2 ± 0.07	2.7 ± ...
400 ± 75*	2450 ± 350**	4550 ± 410**	1500 ± ...
2300 ± 250**	990 ± 170*	–	800 ± ...
120 ± 100*	1095 ± 140	–	1200 ± ...
340 ± 250	1090 ± 230	1350 ± 300	570 ± ...

...nificant changes from the control values (= 0 day). $P < 0.01$.

...vel serum hormones were unchanged, but ... nmol/l ($P < 0.05$) and serum T_4 from 56 ... T_4 remained low at 100 and 500 mg/l ... evel. Serum TSH rose at 100 mg/l from 61... continued to rise to 1490 ng/ml at 500 mg/l ...

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...ons during administration of ...ous times

...was given, serum T_3 fell on the 2nd day from ... remained at this low level for several days.

Serum T_4 fell from 50 to 38 nmol/l ($P < 0.05$) on the 4th day and reached a very low minimum (12.1 nmol/l, $P < 0.01$) on the 9th day. Serum TSH rose from 320 to 2450 ng/l on the 6th day ($P < 0.01$) and increased further to a high maximum of 4550 ng/ml on the 9th day ($P < 0.01$), and then fell to 1500 ng/ml on the 14th day (Table 1).

The weights of anterior pituitaries were increased and the rats had goitres as early as on the 4th day of the PTU-treatment (Table 2).

MMI. – With 5 mg/l of MMI in drinking water, serum TSH rose from 505 to 2300 ng/ml on the 6th day ($P < 0.01$), then fell to 990 and 800 ng/ml on the 9th and 14th day, respectively. The fall in serum T_4 was significant on the 6th ($P < 0.05$) and 14th day ($P < 0.01$). Serum T_3 remained unchanged during the experiment (Table 1).

$KClO_4$. – When 100 mg/l of $KClO_4$ was given, serum TSH rose from 610 to 1120 ng/ml on the 4th day remained at that level. Serum T_3 decreased from 2.0 to 1.0 mmol/l on the 4th and 6th day. Serum T_4 also decreased from the 2nd day but the change was not statistically significant in this experiment (Table 1).

KI. – When KI (100 mg/l) was administered in drinking water, serum TSH rose from 680 to 1460 ng/ml on the 2nd day ($P < 0.05$) but then declined to the initial level. Serum T_4 tended to fall at the beginning of the treatment but increased on the 6th day from 52 to 74.8 nmol/l ($P < 0.05$) and on the 14th day to 52.7 nmol/l ($P < 0.01$). Serum T_3 concentration was decreased on the 2nd day only (Table 1).

Table 2.

The weights of the thyroid and anterior pituitary glands of the rats during administration of PTU (10 mg/l) in drinking water for 4 or 10 days.

	Wet weight (mg/100 g of body weight)	
	Thyroid gland	Anterior pituitary
Control	5.8 ± 0.3	2.6 ± 0.1
4 days on PTU	13.3 ± 0.1**	3.5 ± 0.1*
10 days on PTU	16.0 ± 0.2**	3.4 ± 0.1*

Mean ± SEM of 6 animals in each group. * $P < 0.05$. ** $P < 0.01$ vs. the control rats.

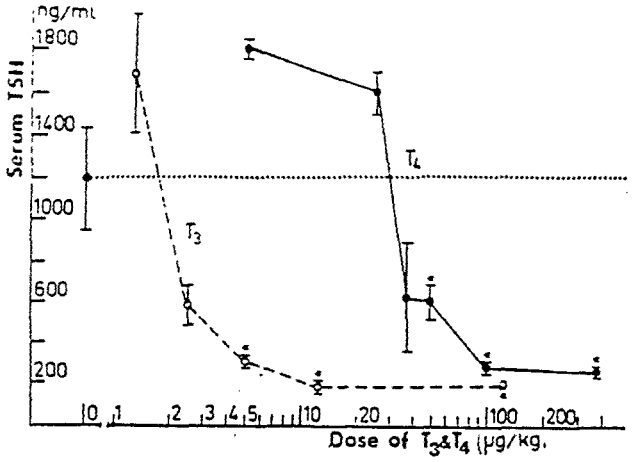


Fig. 4.

Effect of graded doses of T_3 (o----o: 0–125 μg/kg iv; log scale) and T_4 (•——•: 5–375 μg/kg iv; log scale) on the serum TSH levels elevated by a prior PTU treatment (10 mg/l in drinking water for 4 days). The rats were killed 2 h after the injection of saline, T_3 or T_4. n = 4–5 at each dose level. Mean ± SEM. Statistics: ★ $P < 0.05$ vs the PTU control rats (....).

Effects of various manipulations on serum TSH concentration in the PTU-treated animals

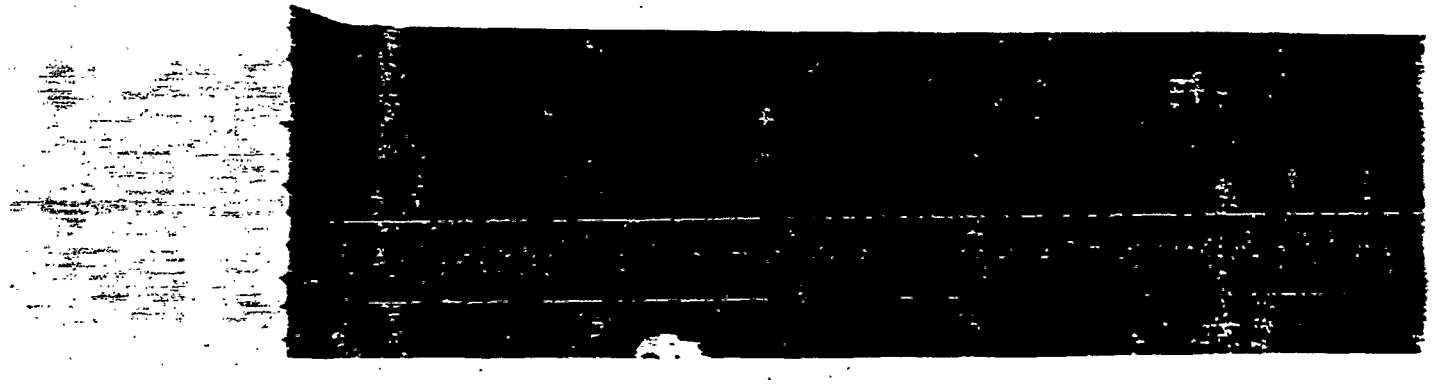
Reproducibility. – When PTU (10 mg/l) was given to groups of 5–7 rats in 3 separate experiments, serum TSH rose from 441 ± 52 to 906 ± 104 ng/ml (mean ± SEM) in 3 days and from 600 ± 51 to 1720 ± 125 ng/ml in 4 days. The respective coefficients of variation in TSH concentrations were 30 % (3 days' treatment) and 16 % (4 days' treatment).

Table 3.

The effect of cold exposure and TRH on the serum TSH levels in the PTU-treated rats (10 mg/l in drinking water for 4 days).

Treatment	Serum TSH (ng/ml)
Water control	446 ± 81
PTU control, 22°C	1173 ± 169
PTU and 30 min at −4°C	2177 ± 277*
PTU and 100 ng of TRH iv	2161 ± 150*

Mean ± SEM of 9–10 animals.
* $P < 0.01$ vs. the PTU control.



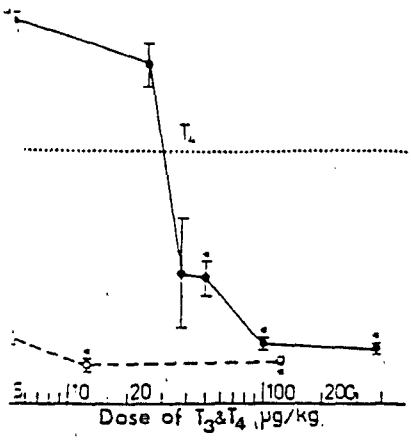


Fig. 4.
–○: 0–125 µg/kg iv; log scale) and T_4 (●
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for 4 days).

	Serum TSH (ng/ml)
	446 ± 81
	1173 ± 169
+4°C	2177 ± 277*
TRH iv	2161 ± 150*

mals.
control.

Effect of thyroid hormones, TRH and cold-exposure. – In the first experiment the rats were given PTU (10 mg/l, 4 days) and then various amounts of I_3 or T_4 iv. Within 2 h small amounts of T_3 (1.7 µg/kg) and T_4 (5–30 µg/kg) did not significantly modify TSH levels but higher doses rapidly decreased the serum TSH levels (Fig. 4). In another experiment the high TSH levels, induced by PTU, were further increased by iv injection of 100 ng of TRH (from 1173 ± 169 to 2177 ± 277 ng/ml, $P < 0.01$) and by transferring the rats from 22 to 4°C for 30 min (to 2210 ± 80 ng/ml, $P < 0.01$) (Table 3).

DISCUSSION

In this study each antithyroid drug induced a different pattern of serum immunoassayable hormone levels at the beginning of treatment. We observed that in the PTU-treated rats T_3 fell and TSH increased early and T_4 decreased later. In the $KClO_4$-treated rats T_3 and T_4 decreased at a parallel rate and TSH levels increased at the same time. Administration of MMI did not affect T_3 at all, and after KI serum T_4 was even increased, although serum TSH levels were at least transiently increased in both cases.

Although in this study serum thyroid hormone levels did not fall *before* the rise in serum TSH, we still believe that these antithyroid drugs primarily decrease either serum T_3 or T_4 or both, which, according to the classical feedback theory, then leads to a rise in serum TSH. We want to point out that in the rats kept on a low iodide diet serum TSH was also increased *before* any detectable change in serum T_3 or T_4 (*Riesco et al.* 1977). The fact that we were not able to observe in all cases significant falls in serum thyroid hormone levels before the rise of serum TSH may be due to the inability of T_3 and T_4 radioimmunoassays to detect minute, but possibly physiologically significant, T_3 and T_4 changes.

In earlier studies antithyroid drugs have been used in drinking water in concentrations of 100–1000 mg/l (*Bakke & Lawrence* 1964; *Wilber & Utiger* 1967; *Liewendahl et al.* 1972; *Griessen & Lemarchand-Béraud* 1973), and those treatments have increased serum TSH levels in 1 day – 4 months. Our results show that these doses are unnecessarily high since significant changes in serum T_3, T_4 and TSH were obtained at doses 10–200 times lower. The disappearance of the initial serum TSH rise in response to PTU (*Griessen & Lemarchand-Béraud* 1973) or thyroidectomy (*Van Rees* 1966) is said to be due to the exhaustion of pituitary TSH reserves. We were able to confirm the transient rise in serum TSH levels even with very low doses of PTU as well as with MMI, and to some extent with KI. On the other hand, $KClO_4$ seemed to be able to stimulate TSH secretion continuously. Possibly the dose was relatively lower than that of PTU and MMI, and did not cause the depletion of pituitary TSH.

It was also demonstrated here that MMI did not affect serum T_3 level, wh was clearly decreased by PTU. This result was not unexpected because su stantial amounts of serum T_3 are derived from serum T_4 by deiodination, an PTU – but not MMI – is known to block this reaction (*Van Arsdel & William* 1956; *Hershman & Van Middlesworth* 1962; *Morreale de Escobar & Escobe del Rey* 1967). We also found that our initial TSH burst was associated wit the fall of either serum T_3 (PTU and $KClO_4$) or T_4 (MMI). It is difficult t say whether T_3 or T_4 is able to inhibit TSH secretion at the anterior pituitar level because there are pituitary receptors for both hormones (*Oppenheime et al.* 1976) but, on the other hand, T_4 is rapidly deiodinated to T_3 in the an terior pituitary (*Silva et al.* 1978).

In this study KI administration also led to the initial TSH burst. Later serur T_4 level began to rise and serum TSH level decline. So it appears that low K doses (about 4 mg/day) initially work antithyroidally but later, perhaps due t increased availability of iodide, T_4 synthesis is increased. There is no previou information about the effects of small doses of iodide on serum TSH but larg doses have slightly increased serum TSH level at 4 months (*Liewendahl et a.* 1972).

The present results prompted us to set up a model in which stimulated TSH secretion can be studied. PTU is given in drinking water (10 mg/l) for 4 day to increase serum TSH levels. The reproducibility of this TSH response is gooc even better than that obtained with the cold-exposed animals (*Tuomisto et a.* 1975; *Männistö et al.* 1978). Our model appears to be useful because elevate TSH levels are further increased in response to cold or to administration o TRH and rapidly decreased by thyroid hormones. Both the TRH-induced an cold-induced TSH responses are well comparable with those observed in th normal rats (*Tuomisto et al.* 1975; *Ranta et al.* 1977; *Männistö et al.* 1978 1979). We have also shown that various drugs can modify the PTU-induce TSH secretion (*Männistö & Ranta* 1978).

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